UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,831	07/07/2004	Frank Karlsen	B0192.70052US00	1388

23628 7590 08/18/2006

WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,831	KARLSEN, FRANK	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,9,16,21,22,25-27 and 29-31* is/are pending in the application.

4a) Of the above claim(s) *8,9,16,21,22,25-27,29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 30* is/are rejected.

7)☒ Claim(s) *1-5, 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Remarks

1. Claims 1-5, 8, 9, 16, 21, 22, 25-27, and 29-31 are currently pending. Claims 1-5 and 30 have been amended. Claims 8, 9, 16, 21, 21, 25-27, 29, and 30 have been withdrawn. It is noted that this action has been made non-final due to the inclusion of new grounds of rejection not necessitated by amendment (the 103 rejection in section 11 below and also the obvious-type double patenting rejection in section 12).

Election/Restrictions

2. This application contains claims 8, 9, 16, 21, 22, 25-27, 29, and 31 drawn to an invention nonelected with traverse in Paper No. 20060103. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

3. Claims 1-5 and 30 are objected to because of the following informalities: The claims recite non-elected SEQ ID Nos. Appropriate correction is required.

Maintained Rejections

Claim Rejections – 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Von Knebel-Doberitz et al. (USPN 6,027,891; cited previously).

Regarding claim 1, Von Knebel-Doberitz teaches an oligonucleotide molecule for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus, where the oligonucleotide is a complement of SEQ ID NO: 20. SEQ ID Nos: 4 and 22 of Von Knebel-Doberitz are oligonucleotide primers of 21 nucleotides that contain the exact complement of the instant SEQ ID No: 20 with the addition of a single thymine nucleotide at the 5' end (see sequence listing). Von Knebel-Doberitz further teaches that SEQ ID No: 4 is a suitable primer for the E6-E7 region of HPV (column 2, line 65 – column 3, line 15). It is noted that the claim recites an oligonucleotide comprising SEQ ID NO: 20, and Von Knebel-Doberitz teaches the complementary sequence in SEQ ID NO: 4. However, in teaching this complementary sequence,

Von Knebel-Doberitz inherently teaches the complement (the instant SEQ ID NO: 20). Therefore, Von Knebel-Doberitz anticipates claim 1.

6. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Anthony et al. (US Pub No. 2004/0214302 A1). This pre-grant publication obtains benefit of Application No. 09/594,839 filed on June 15, 2000.

Regarding claim 1, Anthony teaches an oligonucleotide molecule for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus, the oligonucleotide comprising the instant SEQ ID NO: 20. SEQ ID No: 95 of Anthony is an oligonucleotide of 33 nucleotides that contains the exact sequence of the instant SEQ ID No. 20 with an additional seven nucleotides at the 5' end and an additional six nucleotides at the 3' end (see sequence listing, page 35). This oligonucleotide is also inherently a NASBA P2 primer. Therefore, Anthony anticipates claim 1.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections – 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 2, and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable in view of Shimada et al. (EP 0 402 132 A2; cited previously) in view of Buck et al. (Biotechniques 1999; cited previously) and further in view of Simpkins et al. (Letters in Applied Microbiology (2000); cited previously).

Regarding claims 1, 2, and 4, Shimada teaches an oligonucleotide 20 nucleotides in length that matches exactly the sequence of the instant SEQ ID No: 16 in 18 of 20 nucleotides (see Table 2, sequence p18-3). The only difference between the instant SEQ ID No: 16 and the oligonucleotide of Shimada is the addition of two nucleotides to the 3' end in the instantly claimed oligonucleotide not present in the Shimada oligonucleotide.

Shimada does not teach that the oligonucleotide is modified at the 5' end to contain the T7 promoter sequence GATGCAAGGTCGCATATGAG for use as a NASBA P2 primer.

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck

also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Regarding claims 1, 2, and 4, Simpkins teaches NASBA for the detection of Salmonella enterica using a NASBA P2 primer containing the sequence GATGCAAGGTCGCATATGAG at the 5' end, where the sequence GATGCAAGGTCGCATATGAG is specific for the Nuclisens™ ruthenium-linked oligonucleotide detection probe (see Primers & probes section, page 76). Simpkins further teaches that NASBA using an mRNA template is a more accurate method of quantifying nucleic acids compared to conventional PCR or RT-PCR (see page 75, col. 1 – page 76, col. 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to modify the 3' terminus of the oligonucleotide disclosed by Shimada in order to obtain the instantly claimed oligonucletide of SEQ ID No: 16. As noted above, the differences between the instantly claimed oligonucleotide and the oligonucleotide of Shimada are minor – two additional 3'-terminal nucleotides are present in the instant sequence. Absent any disclosed advantage for using the instantly claimed oligonucleotide, the differences appear to stem from user preference rather than an improvement over the oligonucletide taught by Shimada. Furthermore, since Buck clearly demonstrated the equivalence of primer sequences, the ordinary biochemist could have anticipated a reasonable level of success in using the modified primers to amplify mRNA transcripts from HPV.

Attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 5 of the reference)."

As noted above, the prior art of Shimada teaches an oligonucleotide highly similar to the instant SEQ ID No: 16, with the only difference relating to the addition of two nucleotides at the 3' terminus of the instant sequence. Furthermore, Shimada taught regions of approximately 100 nucleotides designated as useful for primer design for the detection of HPV (Table 1, Sequence 5

(HPV18 from Region II)). Since the claimed primer simply represents a structural homolog, which was derived from sequences suggested by the prior art of Shimada as useful for primers and probes for the detection of HPV, and in particular for detection of transcripts of the E6 gene, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primer is *prima facie* obvious over the cited references in the absence of secondary considerations.

It also would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to modify the oligonucleotide of Shimada to include the T7 promoter sequence GATGCAAGGTCGCATATGAG to permit its use in the NASBA reaction, because Simpkins taught that inclusion of a generic probe sequence in the NASBA P2 primer was useful for detection of the amplified products using electrochemiluminescence (ECL). Moreover, Simpkins taught that NASBA was more useful for amplification of RNA than the PCR amplification method taught by Shimada. One of ordinary skill would have expected the oligonucleotide of Shimada to work reasonably well in a NASBA reaction, because Shimada demonstrated that the oligonucleotide was capable of amplifying HPV, and incorporation of the generic probe sequence GATGCAAGGTCGCATATGAG could have been accomplished using standard synthesis methods known in the art. Therefore, the ordinary practitioner, interested in a more efficient RNA amplification method for detection of mRNA transcripts from HPV, would have been motivated to modify the oligonucleotide of Shimada for use in a NASBA reaction, specifically by incorporating the generic probe sequence GATGCAAGGTCGCATATGAG, as suggested by Simpkins, in order to detect the NASBA products using ECL, thus resulting in the instantly claimed invention.

9. Claims 1, 5, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable in view of Shimada et al. (EP 0 402 132 A2; cited previously) in view of Tyagi et al. (Nature Biotechnology (1996) 14: 303-308; newly cited) and further in view of in view of Buck et al. (Biotechniques (1999); cited previously).

Regarding claims 1 and 5, Shimada teaches an oligonucleotide 20 nucleotides in length that matches exactly the instantly claimed SEQ ID No: 18 in 18 out of a possible 20 nucleotides (see Table 3, sequence p818 II). The oligonucleotide of Shimada contains two additional nucleotides at the 5' end (namely, CC) and lacks three nucleotides at the 3' end (namely, ATG) present in the instantly claimed SEQ ID No: 18.

Shimada does not teach that the sequence is a molecular beacon.

Regading claims 1 and 30, Tyagi taught molecular beacons for rapid, specific detection of amplified nucleic acids. Regarding these probes, Tyagi expressly stated, "The probes are particularly suited for monitoring the synthesis of specific nucleic acids in real time. When used in nucleic acid amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube (abstract)."

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby

testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to modify the oligonucleotide taught by Shimada in order to obtain the instantly claimed oligonucletide of SEQ ID No: 18. As noted above, the differences between the instantly claimed oligonucleotide and the oligonucleotide of Shimada are minor – the Shimada sequence contains an additional two 3'-terminal nucleotides and lacks the first three 5'-terminal nucleotides of the instant sequence. Absent any disclosed advantage for using the instantly claimed oligonucleotide, the differences appear to stem from user preference rather than an improvement over the oligonucletide taught by Shimada. Furthermore, since Buck clearly demonstrated the equivalence of primer sequences, the ordinary biochemist could have

anticipated a reasonable level of success in using the probes (which unlike primers must only hybridize and not undergo extension) taught by Shimada to detect mRNA transcripts from HPV.

Attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 5 of the reference)."

As noted above, the prior art of Shimada teaches an oligonucleotide highly similar to the instant SEQ ID No: 18, with the only differences relating to 2-3 nucleotides at the termini. Furthermore, Shimada taught regions of approximately 100 nucleotides designated as useful for primer design for the detection of HPV (Table 1, Sequence 5 (HPV18 from Region II)). Since the claimed probe simply represents a structural homolog, which was derived from sequences suggested by the prior art of Shimada as useful for primers and probes for the detection of HPV, and in particular for detection of transcripts of the E6 gene, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed probe is *prima facie* obvious over the cited references in the absence of secondary considerations.

It also would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a molecular beacon based on the oligonucleotide of Shimada for detection

of amplified products. Tyagi expressly taught that molecular beacons offered highly specific, sensitive, single-tube, real-time detection of amplified products (see above). The ordinary practitioner would have been motivated by the teachings of Tyagi to modify the probe taught by Shimada to function as a molecular beacon in order to achieve the advantages of beacon detection discussed above. Since Tyagi taught that the required fluorophores were attached to the probe during its chemical synthesis, the skilled artisan would have expected a reasonable level of success in adapting the oligonucleotide of Shimada into a molecular beacon.

10. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Von Knebel-Doberitz et al. (USPN 6,027,891; cited previously) in view of Kievits (J. of Virological Methods, 1991; cited previously) and further in view of Yates et al. (J. of Clinical Microbiology, 2001; cited previously).

Von Knebel-Doberitz teaches the oligonucleotide of claim 1, as discussed above.

Von Knebel-Dobertiz does not teach a NASBA P1 primer comprising the instant SEQ ID NO: 20.

Kievits teaches nucleic acid sequence based amplification (NASBA) as a method for detection of HIV-1 in clinical samples (see abstract). In a review of the principles of the method, Kievits notes the requirement of an RNA polymerase promoter sequence, such as the sequence for the T7 RNA polymerase (AATTCTAATACGACTCACTATAGGG) (see Figures 1 and 2) in order to synthesize the amplified RNA produced by the method.

Yates teaches a method for detecting HBV using NASBA and molecular beacon detection. This method uses a P1 NASBA primer containing the sequence

AATTCTAAATACGACTCACTATAGGGAGAAGG at the 5' end to function as a T7 RNA polymerase promoter sequence (see Table 1, page 3657).

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to modify the oligonucleotide of Von Knebel-Dobritz et al. to contain a T7 RNA polymerase promoter sequence such as AATTCTAAATACGACTCACTATAGGGAGAAGG for use in a NASBA reaction, because Kievits et al. taught that inclusion of such a promoter sequence is essential for conducting the NASBA reaction (see Figures 1 & 2; page 276). Although Kievits taught the use of a promoter sequence that is 6 nucleotides shorter than the instantly claimed sequence, Yates successfully used a NASBA P1 primer containing the longer, instantly claimed sequence, thereby providing the ordinary artisan with an alternative promoter sequence and a reasonable expectation of success in performing NASBA using such a primer. Moreover, Kievits also taught that NASBA has several advantages over the conventional amplification methods taught by Von Knebel-Dobritz, including being more suitable for amplification of RNA target sequences and lacking the need for thermocycling (page 274). Therefore, one of ordinary skill in the art, interested in obtaining a better amplification of mRNA transcripts from the E6 gene of HPV would have been motivated to modify the oligonucleotide of Von Knebel-Dobritz et al. for use in a NASBA reaction by including a T7 RNA polymerase promoter sequence as taught by Kievits or Yates, thus resulting in the instantly claimed invention.

New Grounds of Rejection NOT Necessitated by Amendment

11. Claims 1, 5, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cummins et al. (USPN 5,654,416; cited previously) or Hendricks et al. (WO 91/08312; cited previously) in view of Tyagi et al. (Nature Biotechnology (1996) 14: 303-308).

Regarding claims 1 and 5, Cummins teaches an oligonucleotide (SEQ ID No: 36) 28 nucleotides in length that contains the exact sequence of the instant SEQ ID No: 18 with an additional five nucleotides at the 5' end and two additional nucleotides at the 3' end (see sequence listing, column 43).

Regarding claims 1 and 5, Hendricks teaches a 38 bp oligonucleotide probe for detection of HPV that contains the exact complement of the sequence of the instant SEQ ID No. 18 with an additional seventeen nucleotides at the 5' end (Figure 3, probe no. 18-4). As noted above, a teaching in the prior art of the complement is an inherent teaching of the reverse strand sequence.

Neither Cummins nor Hendricks teaches that the probe is a molecular beacon.

Tyagi taught molecular beacons for rapid, specific detection of amplified nucleic acids. Regarding these probes, Tyagi expressly stated, "The probes are particularly suited for monitoring the synthesis of specific nucleic acids in real time. When used in nucleic acid amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube (abstract)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a molecular beacon based on the oligonucleotide of Cummins or Hendricks for detection of amplified products. Tyagi expressly taught that molecular beacons offered highly specific, sensitive, single-tube, real-time detection of amplified products (see above). The ordinary practitioner would have been motivated by the teachings of Tyagi to modify the probe taught by either Cummins or Hendricks to function as a molecular beacon in order to achieve the advantages of beacon detection discussed above. Since Tyagi taught that the required fluorophores were attached to the probe during its chemical synthesis, the skilled artisan would have expected a reasonable level of success in adapting the oligonucleotide of either Cummins or Hendricks into a molecular beacon.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-5 and 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 12 of copending Application No. 10/500,832. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '832 application recites the instantly claimed SEQ ID Nos: 16, 18, and 20 (see claim 12 of the '832 application, sequences 4-6 in the claim). Claim 12 of the '832 application further teaches modification of SEQ ID NO: 16 and 20 with the claimed promoter sequences (see fourth and fifth sequences in claim 12) . Finally, Claim 10 of the '832 application teaches that the probes are molecular beacons. Therefore, claims 10 and 12 of the '832 application anticipate the instant claims 1-5 and 30.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

14. 101 rejections

Applicant's arguments, see page 7, filed July 3, 2006, with respect to the rejection of claims 1-5 and 30 as lacking utility under 35 U.S.C. 101 have been fully considered and are persuasive. The amendment of the claims to insert the phrase "synthetic or isolated" has overcome the rejection, and therefore, it has been withdrawn.

102 rejections

Applicant's arguments, see page 8, filed July 3, 2006, with respect to the rejection of claims 1 and 2 under 35 U.S.C. 102(b) as anticipated by Von Knebel-Doberitz have been fully

considered. Regarding claim 2, the arguments are persuasive since Von Knebel-Doberitz no longer teaches all of the elements of the amended claim 2. Therefore, the previously made rejection has been withdrawn. Regarding claim 1, however, Applicant's arguments are not persuasive. As discussed above, by teaching an oligonucleotide complementary to the instant SEQ ID NO: 20 (see SEQ ID Nos: 4 & 22 cited above), Von Knebel-Doberitz inherently teaches the complementary sequence corresponding to the instant SEQ ID No: 20. Therefore, Von Knebel-Doberitz continues to anticipate claim 1.

Applicant's arguments, see page 8, filed July 3, 2006, with respect to the rejection of claims 1 and 2 under 35 U.S.C. 102(b) as anticipated by Anthony have been fully considered. Regarding claim 2, the arguments are persuasive since Anthony no longer teaches all of the elements of the amended claim 2. Therefore, the previously made rejection has been withdrawn. However, Applicant's arguments with respect to claim 1 are not persuasive, because, as discussed in greater detail above, SEQ ID No: 95 of Anthony is inherently a NASBA P2 primer. Therefore, the prior art of Anthony continues to anticipate claim 1.

Applicant's arguments, see page 9, filed July 3, 2006, with respect to the rejection of claims 1 and 5 under 35 U.S.C. 102(b) as anticipated by either of Cummins or Hendricks have been fully considered and are persuasive. Neither of the above references teaches molecular beacon probes comprising the instant SEQ ID NO: 18, and therefore, the previously made rejection is withdrawn.

103 rejections

A. Shimada, Buck, & Simpkins

Applicant's arguments with respect to claims 1, 2, and 4 have been considered but are moot in view of the new ground(s) of rejection presented above. However, Applicant does present arguments still relevant to the new rejection presented above, namely: (1) Shimada does not teach SEQ ID Nos: 16 and 18 or suggest which nucleotides should be added to or removed from the disclosed sequences to arrive at Applicant's sequence, (2) the Buck reference is concerned with selection of primers for DNA sequencing, and therefore is not particularly relevant to selection of NASBA primers, and (3) SEQ ID No: 16 is intended for use as a NASBA P2 primer for mRNA amplification, whereas Shimada teaches DNA amplification, and therefore, no suggestion to combine the references exists.

Regarding the first argument, Shimada taught regions of approximately 100 nucleotides designated as useful for primer design for the detection of HPV (Table 1, Sequence 5 (HPV18 from Region II). This teaching would have provided the ordinary practitioner with motivation to design primers based on the disclosed regions in order to effectively detect HPV. Since the entire sequence of the instant SEQ ID NOs: 16 and 18 are contained in this larger region taught by Shimada, the ordinary practitioner would have been provided with suggestion as to what nucleotides to add or remove at the termini. Therefore, Shimada provided the skilled artisan with motivation and suggestion as to the instantly claimed primer sequence, and absent any secondary considerations, this sequence is obvious in view of the cited references.

Regarding the second argument, Applicant correctly states that the Buck reference is directed to the design of DNA sequencing primers rather than NASBA primers. However, the

critical requirement for both types of primers is their ability to undergo extension when hybridized to the target. Since neither a DNA sequencing primer nor a NASBA primer will function if it is unable to undergo extension, the teachings of Buck, that every designed primer worked (i.e. was able to be extended), is highly relevant to the present case. Based on the teachings of Buck, the ordinary artisan would have had a reasonable expectation of success in using any primer designed from the HPV E6 region taught by Shimada.

In response to applicant's third argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed in greater detail in the 103 rejection above, Simpkins teaches that using NASBA to amplify mRNA is a more accurate method of quantifying nucleic acids compared to RT-PCR or PCR amplification (see pages 75-76 cited above). The ordinary practitioner would have been motivated by these teachings of Simpkins to substitute NASBA for PCR in order to improve the accuracy of the results obtained.

B. Von Knebel-Doberitz, Kievits, & Yates

Regarding the rejection of claim 3 under 35 U.S.C. 103(a) as obvious over Von Knebel-Doberitz in view of Kievits and further in view of Yates, Applicant's arguments filed July 3, 2006 have been fully considered but they are not persuasive. Applicant presents two arguments:

(1) since Von Knebel-Doberitz teaches the complement of the instant SEQ ID NO: 20, the combination of Von Knebel-Doberitz, Kievits, and Yates do not produce the claimed invention and (2) the claimed primer would not function in the method of Von Knebel-Doberitz, and therefore, there is no motivation in the cited references leading to the claimed invention.

Regarding the first argument, as discussed above, in teaching an oligonucleotide complementary to the instant SEQ ID NO: 20, Von Knebel-Doberitz inherently taught the complement corresponding to the instantly claimed sequence.

In response to applicant's second argument that the primer of the instant SEQ ID NO: 20 would not function in the method of Von Knebel-Doberitz, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The present invention is not directed to a method of amplifying a specific region of the HPV E6 gene, but simply an oligonucleotide comprising an HPV E6-specific portion and a T7 promoter portion. Von Knebel-Doberitz teaches a region of the E6 gene which may be targeted by an amplification primer (see column 2, line 65 – column 3, line 15; where SEQ ID No: 4 is targeted to the E6 region). The ordinary practitioner would have recognized that this region of the E6 gene could be targeted using a forward primer, as taught by Von Knebel-Doberitz, or a reverse primer (based on the complementary sequence) as instantly claimed. Then, since Kievits and Yates taught the advantages of NASBA compared to conventional PCR (see above), the person of ordinary skill would have been motivated by the

teachings of Kievits and Yates to adapt the primer of Von Knebel-Doberitz for NASBA. This would require addition of a 5' promoter region to the reverse primer. In short, the issue is not whether the primer of the instant SEQ ID No: 20 would amplify the same region as the primer of Von Knebel-Doberitz, but whether the combined teachings of Von Knebel-Doberitz, Kievits, and Yates would have motivated the ordinary practitioner to design the instantly claimed primer. Since Von Knebel-Doberitz taught a particular primer sequence useful for amplifying the HPV E6 gene, differing from the instantly claimed primer in reciting the complement of the instantly claimed sequence and also possessing an additional 5' thymine, and Kievits and Yates taught the advantages of NASBA relative to conventional PCR amplification as well as specific T7 promoters useful in NASBA P1 primers, the ordinary practitioner would have been motivated to design a T7-containing NASBA P1 primer using the promoter portion suggested by Kievits or Yates and either the E6-specific sequence taught by Von Knebel-Doberitz or its complement, thus resulting in the instantly claimed oligonucleotide.

C. Cummings and Hendricks

Applicant's arguments with respect to Cummins and Hendricks references (pages 14-15) have been considered but are moot in view of the new ground(s) of rejection presented above.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Patent Examiner
Art Unit 1637

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
9/11/07